

191



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,882	03/20/2000	JAVIER FARINÁS	UCSF1100-3	7814

28213 7590 06/02/2004

GRAY CARY WARE & FREIDENRICH LLP
4365 EXECUTIVE DRIVE
SUITE 1100
SAN DIEGO, CA 92121-2133

EXAMINER

HUYNH, PHUONG N

ART UNIT	PAPER NUMBER
----------	--------------

1644

DATE MAILED: 06/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/403,882	Applicant(s) FARINAS, JAVIER	
	Examiner Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE Three MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 March 2004.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-2, 5-6, 8-18, 60, 63-65, and 75-80 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1,2,5,6,8-18,60,63-65,75,76,79 and 80 is/are rejected.
- 7) ☒ Claim(s) 77 and 78 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Claims 1-2, 5-6, 8-18, 60, 63-65, and 75-80 are pending.
2. In view of the amendment filed 3/4/04, the following rejections remain.
3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
4. Claims 1-2, 5-6, 8-18, 60, 63-65, 75-76, and 79-80 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for (1) a method for localizing a probe comprising a) contacting a sample comprising a cell expressing a single chain antibody comprising SEQ ID NO: 1 that binds specifically to the ligand PhOx with a membrane permeant probe/ligand conjugate, said probe/ligand conjugate comprising i) a probe moiety such as Bodipy Fl, ii) a ligand such as PhOx that can bind with said single chain antibody and iii) a linker moiety coupling said probe to said ligand wherein the linker is diaminopentane; (2) the said method wherein the probe is a spectroscopic probe; (3) the said method wherein the single chain comprises a fusion protein; (4) the said method wherein said detecting comprises NMR imaging, positron emission tomography or activated cell sorting; (5) the said method wherein the detecting comprises locating the fluorescence characteristic of the fluorescent moiety within the cell, or at least one optical property of the spectroscopic probe such as fluorescence emission, or fluorescence anisotropy; (6) the said method wherein the cell is eukaryotic cell, or a mammalian cell; (7) the said method further comprising the steps of i) adding a stimulus to the cell and ii) detecting the probe/ligand conjugate, before and at least one time after addition of the stimulus; (8) a method for localizing a probe as recited in claim 60 wherein the specific binding partner is a single chain antibody expressed from a recombinant nucleic acid comprising SEQ ID NO: 1; (9) the methods mentioned above wherein the probe provides a more intense signal when the probe/ligand conjugate is bound to the single chain antibody than when it is unbound; (10) the method for localizing a probe within a cell wherein the single chain antibody is bound to a Golgi apparatus membrane or an endoplasmic reticulum membrane, (11) the method for

Art Unit: 1644

localizing a probe within a cell wherein the ligand is selected from the group consisting of phOx, hemagglutinin, Poly His, V5 and myc; (12) the method for localizing a probe within a cell wherein the linker is diaminopentane; (13) the method for localizing a probe within a cell wherein the cell is a living cell, and (14) the method for localizing a probe within a cell wherein the probe is a pH sensitive fluorescent probe; **does not** reasonably provide enablement for a method for localizing a probe within a cell comprising a) contacting a sample comprising a cell expressing *any* single chain antibody with a membrane permeant probe/ligand conjugate, said probe/ligand conjugate comprising i) a probe moiety, ii) *any* ligand that can bind with said single chain antibody and iii) a linker moiety coupling said probe to said ligand wherein said single chain antibody is *any* single chain that has at least “**30% sequence identity**” to SEQ ID NO: 1 or *any* “homologue” of SEQ IDNO: 1, and binds PhOx; a method for localizing a probe as set forth in claim 60 wherein the specific binding partner is any single chain antibody. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only one single chain antibody that binds specifically to PhOx which encoded by a polynucleotide comprising SEQ ID NO: 1 and a specific method for localizing a probe comprising contacting a sample comprising a cell transfected with the polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody that binds specifically to PhOx ligand with a membrane permeant probe Biody Fl conjugated to the ligand PhOx. The probe moiety is coupled to the ligand PhOx via a flexible aliphatic linker such as diaminopentane. The method further comprises the step of adding a stimulus to the cell and detecting said probe/ligand conjugate, before and after addition of the stimulus.

The specification does not teach how to make cell expressing *any* single chain antibody that bind with any ligand, any single chain antibody that has only “**30% sequence identity**” which is 70% difference to SEQ ID NO: 1 and any “**homologue**” of SEQ NO: 1 that binds PhOx for the method for localizing a probe within the cell without the specific amino acid sequence and/or the corresponding polynucleotide. There is insufficient guidance as to the binding specificity of all single chain antibody and all ligand binding partner. There is insufficient guidance as to which amino acids, and the corresponding nucleotides within the full length sequence of SEQ ID NO: 1 to be modified by substitution, deletion or addition and whether the resulting single chain antibody maintains the same binding specificity as the single chain encoded by SEQ ID NO: 1. Given the indefinite number of single chain antibody and ligand, there is insufficient working example demonstrating all undisclosed single chain antibody with only 30% sequence identity to SEQ ID NO: 1 even binds PhOx, in turn, would be useful for a method of localizing all probe within a cell. A sequence with 30% identity means 70% differences. Although the methods for determining the percent identity, such as the computer programs GCG, BLASTP, BLASTN, GeneWorks, MacVector suites NetOGlyc 2.0 and PSORT prediction, the specific conditions used by Applicant was not disclosed. The use of “percent” in conjunction with *any* of the various terms that refer to sequence identity or similarity is a problem because sequence identity between two sequences has no common meaning within the art. The term “percent” is relative and can be defined by the algorithm and parameter values set when using the algorithm used to compare the sequences. The scoring of gaps when comparing one sequence to another introduces uncertainty as to the percent of similarity between two sequences.

Skolnick *et al*, or record, teach that sequence-based methods for function prediction are inadequate and knowing a protein’s structure does not tell one its function (See abstract, in particular).

Ngo *et al*, of record, teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (see Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Art Unit: 1644

Abaza *et al*, of record, teach even a single amino acid substitution outside of an antigenic site on protein can exert drastic effects on the binding specificity of the monoclonal antibody (See entire document, abstract, in particular).

Given the lack of guidance as to which specific residues within SEQ ID NO: 1 can be changed, it is unpredictable to determine which undisclosed polynucleotide sequence with only 30% identity to the full-length polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody or any homologue of SEQ ID NO: 1 will retain its structure and function such as binding specifically to PhOx. Without the specific guidance as to which nucleotides within SEQ ID NO: 1 can be substitute, deleted and yet retains its function, it is unpredictable which undisclosed single chain antibody encoded by the undisclosed polynucleotide would be useful for transfecting the cell, in turn, the cell expressing the undisclosed single chain antibody would still bind to Probe/Ligand conjugate such as PhOx for the claimed method of localizing the probe. Since the specification fails to provide guidance regarding which recombinant nucleic acid residues can tolerate change, it follows that the method for localizing a probe comprising contacting a sample comprising a cell expressing a single chain antibody encoding by nucleic acid that has at least 30 % sequence to SEQ ID NO: 1 or homologue of SEQ ID NO: 1 is not enabled.

For these reasons, the specification as filed fails to enable one skill in the art to practice the invention without undue amount of experimentation. As such, further research would be required to practice the claimed invention.

Applicants' arguments filed 3/4/04 have been fully considered but are not found persuasive.

Applicants' position is that the present disclosure provides working examples of methods for localizing a probe that include an antibody that binds phOx. A skilled artisan will recognize that virtually any antibody/ligand pair combination, of which are known, can be successfully employed in the methods of the pending claims to localize the probe to the vicinity of the ligand, provided that a conjugate that includes in the ligand is membrane permeant. Skilled artisan based on the disclosure of SEQ ID NO: 1 can design variants of this sequence that will also bind phOx.

However, there is insufficient guidance as to the binding specificity of the single chain antibody in claims 1, ligand binding partner in and claim 60 for the claimed method. Further, the specification does not teach how to make cell expressing *any* single

Art Unit: 1644

chain antibody that has only “**30% sequence identity**” or *70% difference* to SEQ ID NO: 1 and any “**homologue**” of SEQ NO: 1 that binds PhOx for the method for localizing a probe within the cell. There is insufficient guidance as to which amino acids, and the corresponding nucleotides within the full length sequence of SEQ ID NO: 1 to be modified by substitution, deletion or addition and whether the resulting single chain antibody maintains the same binding specificity as the single chain encoded by SEQ ID NO: 1.

5. Claims 1-2, 5-6, 8-18, 60, 63-65, 75-76, and 79-80 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) *all* ligand that bind can bind with all single chain antibody (claim 1), (2) all single chain antibody has at least 30% sequence identity to SEQ ID NO: 1 and binds phOx (claim 5), (3) all single chain antibody is a homologue of SEQ ID NO: 1 and binds phOx (claim 6) in the claimed method for localizing a probe within a cell, (4) all ligand that can bind with any specific binding partner such as all single chain antibody and wherein the specific binding partner is expressed from a recombinant nucleic acid (Claim 60-61) for the claimed method of localizing a probe.

The specification discloses only one single chain antibody that binds specifically to PhOx which encoded by a polynucleotide comprising SEQ ID NO: 1 and a specific method for localizing a probe comprising contacting a sample comprising a cell transfected with the polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody that binds specifically to PhOx ligand with a membrane permeant probe Biotinyl conjugated to the ligand PhOx. The probe moiety is coupled to the ligand PhOx via a flexible aliphatic linker such as diaminopentane. The method further comprises the step of adding a stimulus to the cell and detecting said probe/ligand conjugate, before and after addition of the stimulus.

Besides the specific polynucleotide of SEQ ID NO: 1 that encodes for a single chain antibody that binds specifically to PhOx for a method for localizing a probe within the cell, there is insufficient **written description** about the structure associated with function without the polynucleotide sequence of *other* single chain antibody such as

Art Unit: 1644

single chain that has at least 30% sequence identity to SEQ ID NO: 1, homolog of SEQ ID NO: 1 and single chain antibody expressed from a recombinant acid.

Given the indefinite number of ligand and binding partner and the corresponding nucleic acid, there is inadequate written description about the ligand that can bind with any specific binding partner other than SEQ ID NO: 1 and wherein the specific binding partner is expressed from a recombinant nucleic acid. Further, Applicant discloses **only** one single chain antibody that binds specifically to PhOx wherein the single chain antibody is encoded by SEQ ID NO: 1. Given the lack of a written description of *any* additional representative species of polynucleotide encoding the single chain antibody such as single chain at least 30% sequence identity to SEQ ID NO: 1 and homologue of SEQ ID NO: 1 for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Applicants' arguments filed 3/4/04 have been fully considered but are not found persuasive.

Applicants' position is that the pending claims are directed to a methods instead of compositions. The present disclosure provides working examples of methods for localizing a probe within that include a single chain antibody that binds phOx. The specific single chain antibody/ligand pair combination, of which many are known, can be successfully employed in methods of the pending claims to localize the probe to the vicinity of the ligand, provided that the a conjugate that includes the ligand can be membrane permeant. Single chain antibodies are well characterized and can be generated against virtually any ligand using routine methods known in the art. Pending claims do not recite single chain antibodies from a certain species or genera of organisms. The particular specificity or binding properties of the single chain antibody are not critical to the invention, except that the antibody must bind the ligand used on the conjugate. Single chain antibodies with homology or substantial identity to SEQ ID NO: 1 are not a genus of unknown structure defined by nature. Rather one of ordinary skill can readily

Art Unit: 1644

determine whether a sequence has sufficient sequence identity to meet the claimed limitation and retains the ability to bind phOx using standard techniques.

However, the specification discloses only one single chain antibody that binds specifically to PhOx which encoded by a polynucleotide comprising SEQ ID NO: 1 and a specific method for localizing a probe comprising contacting a sample comprising a cell transfected with the polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody that binds specifically to PhOx ligand with a membrane permeant probe Biody Fl conjugated to the ligand PhOx. The probe moiety is coupled to the ligand PhOx via a flexible aliphatic linker such as diaminopetane. The method further comprises the step of adding a stimulus to the cell and detecting said probe/ligand conjugate, before and after addition of the stimulus. Besides the specific polynucleotide of SEQ ID NO: 1 that encodes a single chain antibody that binds specifically to PhOx for the claimed method for localizing a probe within the cell, there is insufficient **written description** about the structure associated with function without the polynucleotide sequence of the *other* single chain antibody such as single chain that has at least 30% sequence identity to SEQ ID NO: 1, homolog of SEQ ID NO: 1 and single chain antibody expressed from a recombinant acid. Likewise, there is inadequate written description about the ligand binding partner wherein the ligand is membrane permeant without the nucleic acid sequence for the claimed method. Given the lack of a written description of *any* additional representative species of polynucleotide encoding the single chain antibody such as single chain at least 30% sequence identity to SEQ ID NO: 1, homologue of SEQ ID NO: 1 and binding partner for the claimed method, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398; *University of Rochester v. G.D. Searle & Co.*, 69 USPQ2d 1886 (CA FC2004).

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Art Unit: 1644

7. Claims 60 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,017,754 (of record, Jan 2000, PTO 892) in view of Haugland *et al* (of record, Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) and WO 93/11120 publication (of record, June 1993, PTO 892).

The '754 patent teaches a method of identifying and selecting a cell to study genes of interest at a cellular level by transfecting a cell such as eukaryotic or mammalian cell CHO cell with plasmids (recombinant nucleic acid) that encode a fusion protein comprising a single chain antibody (scFv) that binds specifically to a ligand such as phOx and a transmembrane domain of the human PDGFR (See column 10, lines 5-12, in particular). The reference single chain antibody comprises a fusion protein that is engineered to include coding sequence for a transmembrane domain of the human platelet derived growth factor receptor (PDGFR) or any membrane anchoring sequence so that when expressed in transfected cells, this fusion protein is anchored to the membrane via the transmembrane domain of the PDGFR so that the single chain is membrane bound (See column 10, line 4-26, in particular). The reference single chain antibody, which is a homologue of SEQ ID NO: 1 has substantial identity to SEQ ID NO: 1 of instant application (See Fig 1A-2, Fig 6, column 1, line 54 bridging column 2 line 1, column 6, line 11, in particular). The '754 patent further teaches that the ligand such as hapten (PhOx) can be conjugated to a spectroscopic probe such as fluorescent (FITC) or other label via a linker moiety such as BSA to form a ligand/probe conjugate such as PhOx-BSA-FITC to allow for identification and selection of the transfected cell shortly after transfection by detecting fluorescence emission which is one of the optical properties of the FITC probe (See column 7, line 8-13, in particular). The reference FITC probe can be detected by fluorescence activated cell sorting by detecting the fluorescence emission. The said ligand (PhOx) binds to the specific binding partner such as the single chain anti-PhOx antibody non-covalently. The '754 patent further teaches that the use of a single-chained antibody (rAB) is advantageous because the smaller size of the single chain coding sequence allows other inserted coding sequence to be longer without losing cloning efficiency since cloning efficiency is inversely related to vector size (See column 10, line 27-31, in particular).

The claimed invention as recited in claims 64, and 65 differs from the reference only by the recitation of the method wherein the probe provides a more intense signal

Art Unit: 1644

when the probe/ligand conjugate is bound to the single chain antibody than when it is unbound.

Haugland *et al* teach a membrane permeant probe such as BODIPY FL-X (See page 13-14, in particular) that contains a flexible linker such as succinimidyl esters (page 14, column 2, first full paragraph, in particular) which is a non-ionic linker since the reference BODIPY conjugates tend to be more permeant to live cells than are conjugated of charged fluorospores (See page 14, column 2, Last full paragraph, in particular). Haugland *et al* further teach spectroscopic probes such as fluorescein, rhodamine, tetramethylrhodamine (See page 13-14, in particular). The reference BODIPY FL probe as a fluorescein substitute has excitation/emission maxima at 503 and 512 nm, respectively. Haugland *et al* teach that BODIPY conjugates tend to be more membrane permeant to live cells than are conjugates of charged fluorophores (See page 14, column 2, in particular). The reference fluorescent moiety is detected by confocal laser scanning microscopy, fluorescence microscope or flow cytometry application (fluorescence activated cell sorting) which all measure the fluorescence emission, the optical property of the probe (See page 19, in particular). Haugland *et al* further teach a method of linking the BODIPY FL dye to various protein, nucleotides (See page 15, in particular) and the probe is particularly useful for preparing conjugates of peptides, nucleotides, drugs, toxins, and other low molecular weight ligands (See page 14, column 2, second paragraph, in particular). The advantages of BODIPY FL are: (1) the spectra are insensitive to solvent polarity and pH; (2) the narrow emission bandwidth improves peak intensity over that of fluorescein; (3) little or no spectral overlap with longer wavelength dyes such as tetramethylrhodamine; and (4) greater photostability than fluorescein (See page 256, Fig 1, page 262, column 2, in particular).

WO 93/11120 publication teaches a flexible aliphatic linker such as the ϵ aliphatic amino group of lysine for site-selective delivery of therapeutic agent and retention thereof at the selected sites (See page 28, lines 11-32, in particular). The reference flexible aliphatic linker is lipophilic which is membrane permeant (See page 28, 12, in particular). WO 93/11120 publication teaches the N-hydroxy-succinimidyl ester derivatized linker is a particularly good reagent for reaction with lysine since the amide conjugates are very stable (See page 29, lines 4-7, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the nonmembrane permeant linker probe

Art Unit: 1644

conjugate such as BSA-FITC as taught by the '754 patent for the cell permeant probe linker cognate such as BIODIPY FL-X as taught by Haugland *et al* wherein the probe is coupling to the ligand via a linker moiety such as the flexible linker succinimidyl esters as taught by Haugland *et al* or the ϵ aliphatic amino group of lysine linker as taught by the WO 93/11120 publication for a method of detecting a probe as taught by the '754 patent, Haugland *et al* and the WO 93/11120 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Haugland *et al* teach the advantages of BODIPY FL probe are: (1) the spectra are insensitive to solvent polarity and pH; (2) the narrow emission bandwidth improves peak intensity over that of fluorescein; (3) little or no spectral overlap with longer wavelength dyes such as tetramethylrhodamine; (4) greater photostability than fluorescein (See page 256, Fig 1, page 262, column 2, in particular); and (5) useful for preparing conjugates of peptides, nucleotides, drugs, toxins, and other low molecular weight ligands for studies of cell physiology (See page 14, column 2, second paragraph, in particular). The WO 93/11120 publication teaches a flexible aliphatic linker such as the ϵ aliphatic amino group of lysine is useful for site-selective delivery of therapeutic agent and retention thereof at the selected sites (See page 28, lines 11-32, in particular) and the N-hydroxy-succinimidyl ester derivatized linker is a particularly good reagent for reaction with lysine since the amide conjugates are very stable (See page 29, lines 4-7, in particular). The '754 patent teaches that the use of a single-chained antibody (rAB) is advantageous because the smaller size of the single chain coding sequence allows other inserted coding sequence to be longer without losing cloning efficiency since cloning efficiency is inversely related to vector size (See column 10, line 27-31, in particular). Claim 11 is included in this rejection because the cell permeant probe such as BIODIPY FL as taught by Haugland *et al*, which can be located within the cell since it is membrane permeable. Claims 64, and 65 are included in this rejection because the intensity of the signal is an inherent properties of the reference probes and detection of intensity is within the purview of one skilled in the art at the made to detect fluorescent intensity as taught by as taught by the '754 patent, Haugland *et al*. Claim 5 is included in this rejection because the reference is at least 30% identical to

Art Unit: 1644

the claimed SEQ ID NO: 1 since the reference sequence is capable of recognizing PhOx as taught by the '754 patent.

Applicants' arguments filed 3/4/04 have been fully considered but are not found persuasive.

Applicants' position is that the combination of the '754 and the cited secondary references, does not result in a method for localizing a probe within a cell.

However, claim 60 does not recite a method for localizing a probe within a cell.

8. The following new grounds of objection and rejections are necessitated by the amendment filed 3/4/04.
9. Claims 9-16 are objected to because said claims depended from canceled claim 3.
10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:
A person shall be entitled to a patent unless:
(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.
11. Claims 1-2, 5-6, 8, 11-14, 16-17, 64-65 and 75-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,017,754 (of record, Jan 2000, PTO 892) in view of Schouten *et al* (Plan Mol Biol 30(4): 781-93, Feb 1996; PTO 892), Haugland *et al* (of record, Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) and WO 93/11120 publication (of record, June 1993, PTO 892).

The '754 patent teaches a method of identifying and selecting a cell to study genes of interest at a cellular level by transfecting a cell such as eukaryotic or mammalian cell CHO cell with plasmids (recombinant nucleic acid) that encode a fusion protein comprising a single chain antibody (sFv) that binds specifically to a ligand such as phOx and a transmembrane domain of the human PDGFR that target the reference single chain antibody the membrane on the cell surface (See column 10, lines 5-12, in particular). The reference single chain antibody comprises a fusion protein that is engineered to include coding sequence for a transmembrane domain of the human platelet derived growth

factor receptor (PDGFR) or any membrane anchoring sequence so that when expressed in transfected cells, this fusion protein is anchored to the membrane via the transmembrane domain of the PDGFR so that the single chain is membrane bound (See column 10, line 4-26, in particular). The reference single chain antibody, which is a homologue of SEQ ID NO: 1 has substantial identity to SEQ ID NO: 1 of instant application (See Fig 1A-2, Fig 6, column 1, line 54 bridging column 2 line 1, column 6, line 11, in particular). The '754 patent further teaches that the ligand such as hapten (PhOx) can be conjugated to a spectroscopic probe such as fluorescent (FITC) or other label via a linker moiety such as BSA to form a ligand/probe conjugate such as PhOx-BSA-FITC to allow for identification and selection of the transfected cell shortly after transfection by detecting fluorescence emission which is one of the optical properties of the FITC probe (See column 7, line 8-13, in particular). The reference FITC probe can be detect by fluorescence activated cell sorting by detecting the fluorescence emission. The said ligand (PhOx) binds to the specific binding partner such as the single chain anti-PhOx antibody non-covalently. The '754 patent further teaches that the use of a single-chained antibody (rAB) is advantageous because the smaller size of the single chain coding sequence allows other inserted coding sequence to be longer without losing cloning efficiency since cloning efficiency is inversely related to vector size (See column 10, line 27-31, in particular).

The claimed invention as recited in claim 1 differs from the reference only by the recitation that the method for localizing a probe *within a cell* comprising contacting a sample comprising a cell expressing a membrane bound single chain antibody with a membrane *permeant probe/ligand conjugate*, the probe/ligand conjugate comprising a probe moiety, a ligand that can bind with the single chain antibody and a linker moiety coupling the probe to the ligand and detecting the probe/ligand conjugate within the cell, thereby localizing the probe within the cell.

Schouten *et al* teach a method of targeting single chain antibody (scFv) to the various subcellular location by providing various targeting signals such as the endoplasmic reticulum (ER) retention signal sequence KDEL fused to the scFv antibody and expressing the reference scFv expressing the reference antibody in a transgenic plant (See abstract, in particular). The advantage of the KDEL sequence also stabilizes the single chain antibody (See page 791, col. 2, in particular).

Haugland *et al* teach a membrane permeant probe such as BODIPY FL-X (See page 13-14, in particular) that contains a flexible linker such as succinimidyl esters (page 14, column 2, first full paragraph, in particular) which is a non-ionic linker since the reference BODIPY conjugates tend to be more permeant to live cells than are conjugates of charged fluorophores (See page 14, column 2, Last full paragraph, in particular). Haugland *et al* further teach spectroscopic probes such as fluorescein, rhodamine, tetramethylrhodamine (See page 13-14, in particular). The reference BODIPY FL probe as a fluorescein substitute has excitation/emission maxima at 503 and 512 nm, respectively. Haugland *et al* teach that BODIPY conjugates tend to be more membrane permeant to live cells than are conjugates of charged fluorophores (See page 14, column 2, in particular). The reference fluorescent moiety is detected by confocal laser scanning microscopy, fluorescence microscope or flow cytometry application (fluorescence activated cell sorting) which all measure the fluorescence emission, the optical property of the probe (See page 19, in particular). Haugland *et al* further teach a method of linking the BODIPY FL dye to various protein, nucleotides (See page 15, in particular) and the probe is particularly useful for preparing conjugates of peptides, nucleotides, drugs, toxins, and other low molecular weight ligands (See page 14, column 2, second paragraph, in particular). The advantages of BODIPY FL are: (1) the spectra are insensitive to solvent polarity and pH; (2) the narrow emission bandwidth improves peak intensity over that of fluorescein; (3) little or no spectral overlap with longer wavelength dyes such as tetramethylrhodamine; and (4) greater photostability than fluorescein (See page 256, Fig 1, page 262, column 2, in particular).

WO 93/11120 publication teaches a flexible aliphatic linker such as the ϵ aliphatic amino group of lysine for site-selective delivery of therapeutic agent and retention thereof at the selected sites (See page 28, lines 11-32, in particular). The reference flexible aliphatic linker is lipophilic which is membrane permeant (See page 28, 12, in particular). WO 93/11120 publication teaches the N-hydroxy-succinimidyl ester derivatized linker is a particularly good reagent for reaction with lysine since the amide conjugates are very stable (See page 29, lines 4-7, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the transmembrane domain of the human platelet derived growth factor receptor (PDGFR) in the plasmids (recombinant nucleic acid) that encodes a fusion protein comprising a single chain antibody (sFv) that binds

Art Unit: 1644

specifically to a ligand such as phOx and a transmembrane domain of the human PDGFR as taught by the '754 patent for the KDEL sequence that target any scFv to the ER as taught by Schouten *et al* in addition to substituting the nonmembrane permeant linker probe conjugate such as BSA-FITC as taught by the '754 patent for the cell permeant probe linker cognate such as BODIPY FL-X as taught by Haugland *et al* wherein the probe is coupling to the ligand via a linker moiety such as the flexible linker succinimidyl esters as taught by Haugland *et al* or the ϵ aliphatic amino group of lysine linker as taught by the WO 93/11120 publication for a method of detecting a probe within a cell as taught by the '754 patent, Schouten *et al* Haugland *et al* and the WO 93/11120 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '754 patent teaches that the use of a single-chained antibody (rAB) is advantageous because the smaller size of the single chain coding sequence allows other inserted coding sequence to be much longer without losing cloning efficiency since cloning efficiency is inversely related to vector size (See column 10, line 27-31, in particular) and the transmembrane domain could be any membrane anchoring sequence so that when expressed in transfected cells, this fusion protein is anchored to the membrane (See column 10, line 4-26, in particular). Schouten *et al* teach adding various targeting signals such as the endoplasmic reticulum (ER) retention signal sequence KDEL fused to any scFv antibody would target the antibody to the ER within the cell. Haugland *et al* teach the advantages of BODIPY FL probe are: (1) the spectra are insensitive to solvent polarity and pH; (2) the narrow emission bandwidth improves peak intensity over that of fluorescein; (3) little or no spectral overlap with longer wavelength dyes such as tetramethylrhodamine; (4) greater photostability than fluorescein (See page 256, Fig 1, page 262, column 2, in particular); and (5) useful for preparing conjugates of peptides, nucleotides, drugs, toxins, and other low molecular weight ligands for studies of cell physiology (See page 14, column 2, second paragraph, in particular). The WO 93/11120 publication teaches a flexible aliphatic linker such as the ϵ aliphatic amino group of lysine is useful for site-selective delivery of therapeutic agent and retention thereof at the selected sites (See page 28, lines 11-32, in particular) and the N-hydroxy-succinimidyl ester derivatized linker is a particularly good reagent for reaction with lysine since the amide conjugates are very stable (See page 29, lines 4-7, in

Art Unit: 1644

particular). Claim 11 is included in this rejection because the cell permeant probe such as BIODIPY FL as taught by Haugland *et al*, which can be located within the cell since it is membrane permeable. Claim 5 is included in this rejection because the reference is at least 30% identical to the claimed SEQ ID NO: 1 since the reference sequence is capable of recognizing PhOx as taught by the '754 patent. Claims 64-65 are included in this rejection because it is obvious that the signal is more intense when the probe (signal) conjugated to the ligand (phOx) binds to single chain antibody because of localization than when the probe/ligand is scatter and not binds to its partner.

12. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,017,754 (of record, Jan 2000, PTO 892) in view of Schouten *et al* (Plan Mol Biol 30(4): 781-93, Feb 1996; PTO 892), Haugland *et al* (of record, Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) and WO 93/11120 publication (of record, June 1993, PTO 892) as applied to claims 1-2, 5-6, 8, 11-14, 16-17, 64-65 and 75-76 mentioned above and further in view of U. S. Pat No. 5,628,982 (of record, May 1997; PTO 892).

The combined teachings of the '754 patent, Schouten *et al*, Haugland *et al* and the WO 93/11120 publication have been discussed supra.

The claimed invention in claim 9 differs from the combined teachings of the references only in that the method wherein the detecting is by means of NMR imaging.

The '982 patent teaches a probe such as hydroxyl-aryl metal chelates as NMR contrast agents or probes for diagnostic NMR imaging. By incorporating 2-hydroxy-aryl groups into the metal chelating ligand, the metal ion chelate NMR contrast agents (ligands) are produced which preferentially bind to specific proteins (the binding partners) in a non-covalent manner and hence the binding of the affinity of the metal chelate to the protein or distribution is enhanced (See column 1, Summary of Invention, column 15, line 38, in particular). The advantages of gadolinium ion with seven unpaired electrons are: (1) it can be used with a chelating agent having a number of open sites; (2) it can act as a contrast agent at very low dosages; (3) it can be no more toxic than iron used with a chelating agent having no open sites as taught by the '892 patent (See column 15, line 29-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Probe such as FITC as taught by the '764 or

Art Unit: 1644

the probe such as the BODIPY FL dye Haugland *et al* for the hydroxy-aryl metal chelates as NMR contrast agents for NMR imaging as taught by the '982 patent for a method of detecting a probe within a cell as taught by the '754 patent, Schouten *et al*, Haugland *et al* and the WO 93/11120 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the '982 patent teaches the advantages of gadolinium ion with seven unpaired electrons are: (1) it can be used with a chelating agent having a number of open sites; (2) it can act as a contrast agent at very low dosages; (3) it can be no more toxic than iron used with a chelating agent having no open sites and is a useful NMR contrast agents or probes for diagnostic NMR imaging. (See column 15, line 29-34, in particular).

13. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,017,754 (of record, Jan 2000, PTO 892) in view of Schouten *et al* (Plan Mol Biol 30(4): 781-93, Feb 1996; PTO 892), Haugland *et al* (of record, Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) and WO 93/11120 publication (of record, June 1993, PTO 892) as applied to claims 1-2, 5-6, 8, 11-14, 16-17, 64-65 and 75-76 mentioned above and further in view of U.S. Pat No. 5,324,502 (of record, June 1994; PTO 892).

The combined teachings of the '754 patent, Schouten *et al*, Haugland *et al* and the WO 93/11120 publication have been discussed supra.

The claimed invention in claim 10 differs from the combined teachings of the references only in that the method wherein the detecting is positron emission tomography.

The '502 patent teaches a membrane permeant probe such as positron emitting gallium-68(III) cationic complex or lipophilic complex for positron emission tomography (PET). The advantage of radiopharmaceutical has the properties of prolonged retention in the targeted tissue relative to the blood levels and relative to radiopharmaceutical concentration in the adjacent non-targeted tissues (See column 1, line 61-66, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Probe such as FITC as taught by the '764 or the probe such as the BODIPY FL dye Haugland *et al* for the positron emitting gallium-68(III) cationic complex or lipophilic complex taught by the '502 patent for positron emission tomography (PET) detection for a method of detecting a probe as taught by the '754 patent, Haugland *et al* and the WO 93/11120 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because the advantage of radiopharmaceutical has the properties of prolonged retention in the targeted tissue relative to the blood levels and relative to radiopharmaceutical concentration in the adjacent non-targeted tissues as taught by the '502 patent (See column 1, line 61-66, in particular).

14. Claims 15, and 79-80 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,017,754 (of record, Jan 2000, PTO 892) in view of Schouten *et al* (Plan Mol Biol 30(4): 781-93, Feb 1996; PTO 892), Haugland *et al* (of record, Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) and WO 93/11120 publication (of record, June 1993, PTO 892) as applied to claims 1-2, 5-6, 8, 11-14, 16-17, 64-65 and 75-76 mentioned above and further in view of Rizzuto *et al* (of record, Current Biology 5(6): 635-642, 1995; PTO 892) and Kneen *et al* (Biophysical J 74: 1591-1599, March 1998; PTO 892).

The combined teachings of the '754 patent, Schouten *et al*, Haugland *et al* and the WO 93/11120 publication have been discussed supra.

The claimed invention in claim 15 differs from the combined teachings of the references only in that the method further comprises the steps of adding a stimulus to said cell and ii) detecting said probe/ligand conjugate, before and at least one time after addition of said stimulus.

The claimed invention in claim 79 differs from the combined teachings of the references only in that the method wherein the cell is a living cell.

The claimed invention in claim 80 differs from the combined teachings of the references only in that the method wherein the probe is a pH sensitive fluorescent probe.

Rizzuto *et al* teach a method of localizing a probe comprising contacting a sample comprising a cell expressing a probe such as recombinant green fluorescent protein (GFP) of *Aequorea victoria* as a tool for visualizing subcellular organelles in living cells. The reference further teaches adding a stimulus (noradrenaline and histamine) to said cell and detecting the GFP conjugate before and after addition of said stimulus (See page 639-640, Use of GFP in physiological experiments, in particular) and localizing the probe (See page 637, 639, in particular). Rizzuto *et al* further teach the reporter protein can be molecular engineered to include targeting sequences which can cause them to be specifically addressed to the subcellular compartment of interest that is a useful too for monitoring cell physiology in intact living cells in response to stimulus (See abstract, in particular).

Kneen *et al* teach green fluorescent protein (GFP) is a noninvasive intracellular pH indicator and is useful as a pH sensor in living cells (See page 1591, col. 2, second paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add a stimulus to said cell before and at least one time after addition of said stimulus as taught by Rizzuto *et al* and detecting said probe/ligand conjugate for a method of detecting a probe as taught by the '754 patent, Schouten *et al*, Haugland *et al* and the WO 93/11120 publication. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Rizzuto *et al* teach the reporter protein can be molecular engineered to include targeting sequences which can cause them to be specifically addressed to the subcellular compartment of interest and is a useful too for monitoring cell physiology in intact living cells in response to stimulus (See abstract, in particular). Kneen *et al* teach green fluorescent protein (GFP) is a noninvasive intracellular pH indicator and is useful as a pH sensor in living cells (See page 1591, col. 2, second paragraph, in particular).

Art Unit: 1644

15. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over US Pat No. 6,017,754 (of record, Jan 2000, PTO 892) in view of Haugland *et al* (of record, Handbook of Fluorescent Probes and Research Chemicals 6th edition, 1996, pages 13-15, 18-19; PTO 892) and WO 93/11120 publication (of record, June 1993, PTO 892) as applied to claims 1-2, 5-6, 8, 11-14, 16-17, 64-65 and 75-76 mentioned above and further in view of Youn *et al* (of record, Analytical Biochemistry 232: 24-30, 1995; PTO 892).

The combined teachings of the '754 patent, Schouten *et al*, Haugland *et al* and the WO 93/11120 publication have been discussed supra.

The claimed invention in claim 18 differs from the combined teachings of the references only in that the method wherein the optical properties is fluorescence anisotropy.

Youn *et al*. teach a cell permeant probe such as [Ru(bpy)₂(phen-ITC)]²⁺ for a method of detecting probe using fluorescence energy transfer immunoassay (FRET) based on the use of a ruthenium metal ligand complex. In this assay, the human serum albumin (the ligand) is covalently labeled with the donor [Ru(bpy)₂(phen-ITC)]²⁺ and the anti-human serum albumin antibody (the receptor) is labeled with the acceptor reactive Blue 4. Upon binding of the acceptor-labeled antibody (specific binding partner) to the Ru-labeled antigen (ligand), the intensity and decay time of ruthenium metal ligand complex decrease while the anisotropy increases (See page 25, column 2, page 27, Figs 3 & 4, Table 1, in particular). One of the advantages of the Ru complex is its long decay time; since it is chemically and photochemically stable, it allows off-gating of the interfering auto fluorescence and thereby increases the sensitivity of the time-resolved immunoassays. The FRET assay is more reliable because the decay times of the Ru complex are mostly independent of the overall intensity of the emission. Finally, the long decay time of the Ru complexes can be measured with simple instrumentation, and allow the measurement of rotational correlation times up to 1 μ s (See page 24-25, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the Probe such as FITC as taught by the '764 or the probe such as the BODIPY FL dye Haugland *et al* for the cell permeant probe such as [Ru(bpy)₂(phen-ITC)]²⁺ which is detected by fluorescence energy transfer (fluorescence anisotropy) as taught by Youn *et al* as a method of detecting a probe within the cell as taught by the '754 patent, Schouten *et al*, Haugland *et al* and the WO 93/11120 publication. From the combined teachings of the references, it is apparent that one of

Art Unit: 1644

ordinary skill in the art would have had a reasonable of success in producing the claimed invention.

One having ordinary skill in the art at the time the invention was made would have been motivated to do this because Youn *et al* teach the $[\text{Ru}(\text{bpy})_2(\text{phen-ITC})]^{2+}$ complex is its long decay time, chemically and photochemically stable which allows off-gating of the interfering auto fluorescence and thereby increases the sensitivity of the time-resolved immunoassays (See pages 24-25 and 29, in particular). The long decay time of the Ru complexes can be measured with simple instrumentation, and allow the measurement of rotational correlation times up to 1 μs (See page 24-25, in particular).

16. Claims 77-78 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.
17. No claim is allowed.
18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor,

Art Unit: 1644

Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (703) 872-9306.

20. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Phuong N. Huynh, Ph.D.

Patent Examiner

Technology Center 1600

June 1, 2004


CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600